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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,194	06/22/2001	Kimberly F. Glassman	BB1449 US NA	9205

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EXAMINER	
LACOURCIERE, KAREN A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/14/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/887,194	GLASSMAN ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *3-5,13-15 and 20-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 6-12, 16-19, 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I and SEQ ID NO: 13 in Paper No. 11 is acknowledged.

Claims 3-5, 13-15 and 20-44 and SEQ ID NO:12 and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). Provisional Application 60/213,961 has not been identified in the first line of the specification.

Sequence Listing

Applicant should note, the Office has corrected the computer readable format of the sequence listing by deleting non-ASCII "garbage" at the end of the files. No action is required on the part of Applicant with regard to the sequence listing.

Claim Objections

Claim 1 is objected to because of the following informalities: A comma should be inserted after the word "host" in line two of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 6-12, 16-19 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and claims dependent upon claim 1 are indefinite due to the recitation of regions in proximity to "(a)", however, "(a)" is not an object, but rather is a description of a physical characteristic. It is unclear how complementary RNA's can be in proximity to "homology", therefore the claim is indefinite.

Claim 1 and claims dependent upon claim 1 are indefinite due to the recitation "complementary". It is unclear whether "complementary" requires the sequence to be

fully complementary, or whether it would encompass RNA regions with partial complementarity.

Claim 1 recites the limitation "the expressed RNA" in line 6 of the claim. There is insufficient antecedent basis for this limitation in the claim, which renders claim 1 and claims dependent upon claim 1 indefinite.

Claim 1 and claims dependent upon claim 1 are indefinite due to the recitation "substantially similar". It is unclear what degree of similarity must exist between a gene and another endogenous gene to be considered "substantially similar".

Claim 1 and claims dependent upon claim 1 are indefinite because claim 1 recites two features, (a) and (b), however, the claim does recite a conjunction between (a) and (b) and, therefore, it is unclear, for example, whether these features are meant in the alternative or if both characteristics are required.

Claim 1 and claims dependent upon claim 1 are indefinite due to the recitation "unrelated to any endogenous RNA in the host". The metes and bounds of "unrelated" are unclear, for example, how different does an RNA need to be to be considered "unrelated" to any endogenous host gene, what degree of similarity would be considered "related" to an endogenous host gene.

Claim 2 and claims dependent upon claim 2 are indefinite because claim 2 recites RNA regions located 5' or 3' to "(a)", however, "(a)" is not an object, but rather is a description of a physical characteristic. It is unclear how RNA regions can be located 5' or 3' to "homology", therefore the claim is indefinite.

Claim 2 recites the limitation "the RNA in (b)" in line 6 of the claim. There is insufficient antecedent basis for this limitation in the claim, because (b) recites two RNA's, "an RNA region" and "endogenous RNA".

Claim 2 recites the limitation "the expressed RNA" in line 7 of the claim. There is insufficient antecedent basis for this limitation in the claim, which renders claim 2 and claims dependent upon claim 2 indefinite.

Claim 2 and claims dependent upon claim 2 are indefinite due to the recitation "substantially similar". It is unclear what degree of similarity must exist between a gene and another endogenous gene to be considered "substantially similar".

Claim 2 and claims dependent upon claim 2 are indefinite due to the recitation "unrelated to any endogenous RNA in the host". The metes and bounds of "unrelated" are unclear, for example, how different does an RNA need to be to be considered "unrelated" to any endogenous host gene, what degree of similarity would be considered "related" to an endogenous host gene.

Claim 6 and claims dependent upon claim 6 are indefinite due to the recitation "unrelated to any endogenous RNA in the host". The metes and bounds of "unrelated" are unclear, for example, how different does an RNA need to be to be considered "unrelated" to any endogenous host gene, what degree of similarity would be considered "related" to an endogenous host gene.

Claim 6 and claims dependent upon claim 6 are indefinite due to the recitation "a synthetic, non-naturally occurring RNA sequence". It is unclear what characteristics of an RNA would make it synthetic and non-naturally occurring, for example, the RNA of

claim 6 is expressed by a vector in a cell, it is unclear how a portion of the RNA would be "synthetic" or "non-naturally occurring".

Claim 7 and claims dependent upon claim 7 are indefinite due to the recitation "unrelated to any endogenous RNA in the host". The metes and bounds of "unrelated" are unclear, for example, how different does an RNA need to be to be considered "unrelated" to any endogenous host gene, what degree of similarity would be considered "related" to an endogenous host gene.

Claim 8 is indefinite due to the recitation "substantially similar". It is unclear what degree of similarity must exist between a gene and another endogenous gene to be considered "substantially similar".

Claim 9 is indefinite due to the recitation "substantially similar". It is unclear what degree of similarity must exist between a gene and another endogenous gene to be considered "substantially similar".

Claim 10 is indefinite due to the recitation "substantially similar". It is unclear what degree of similarity must exist between a gene and another endogenous gene to be considered "substantially similar".

Claim 11 and claims dependent upon claim 11 are indefinite due to the recitation of regions in proximity to "(a)", however, "(a)" is not an object, but rather is a description of a physical characteristic. It is unclear how complementary RNA's can be in proximity to "homology", therefore the claim is indefinite.

Claim 11 and claims dependent upon claim 11 are indefinite due to the recitation "complementary". It is unclear whether "complementary" requires the sequence to be

fully complementary, or whether it would encompass RNA regions with partial complementarity.

Claim 11 recites the limitation "the RNA" in line 5 of the claim. There is insufficient antecedent basis for this limitation in the claim, because claim 11 recites more than one RNA.

Claim 11 and claims dependent upon claim 11 are indefinite due to the recitation "substantially similar". It is unclear what degree of similarity must exist between a gene and another endogenous gene to be considered "substantially similar".

Claim 11 and claims dependent upon claim 11 are indefinite because claim 1 recites two features, (a) and (b), however, the claim does recite a conjunction between (a) and (b) and, therefore, it is unclear, for example, whether these features are meant in the alternative or if both characteristics are required.

Claim 12 and claims dependent upon claim 12 are indefinite because claim 12 recites RNA regions located 5' or 3' to "(a)", however, "(a)" is not an object, but rather is a description of a physical characteristic. It is unclear how RNA regions can be located 5' or 3' to "homology", therefore the claim is indefinite.

Claim 12 recites the limitation "the RNA in (b)" in line 5 of the claim. There is insufficient antecedent basis for this limitation in the claim, because (b) recites two RNA's, "an RNA region" and "endogenous RNA".

Claim 12 recites the limitation "the RNA" in line 6 of the claim. There is insufficient antecedent basis for this limitation in the claim, because claim 12 recites more than one RNA and it is unclear which RNA is being referred to.

Claim 12 and claims dependent upon claim 12 are indefinite due to the recitation "substantially similar". It is unclear what degree of similarity must exist between a gene and another endogenous gene to be considered "substantially similar".

Claim 16 and claims dependent upon claim 16 are indefinite due to the recitation "unrelated to any endogenous RNA in the host". The metes and bounds of "unrelated" are unclear, for example, how different does an RNA need to be to be considered "unrelated" to any endogenous host gene, what degree of similarity would be considered "related" to an endogenous host gene.

Claim 16 and claims dependent upon claim 16 are indefinite due to the recitation "a synthetic, non-naturally occurring RNA sequence". It is unclear what characteristics of an RNA would make it "synthetic" and "non-naturally occurring".

Claim 17 is indefinite due to the recitation "unrelated to any endogenous RNA in the host". The metes and bounds of "unrelated" are unclear, for example, how different does an RNA need to be to be considered "unrelated" to any endogenous host gene, what degree of similarity would be considered "related" to an endogenous host gene.

Claim 19 is indefinite due to the recitation "substantially similar". It is unclear what degree of similarity must exist between a gene and another endogenous gene to be considered "substantially similar".

Claim 45 recites the limitation "the two complementary RNA sequences" in line two of the claim. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-10 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of reducing the expression of a target gene in a host cell in vitro (cell culture) or in a plant, does not reasonably provide enablement for methods of reducing expression of a target RNA in a host or host cell in vivo (whole organism) in a vertebrate organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 8-10 and 18-20 are drawn broadly to methods of reducing the expression of a target mRNA in generally any host cell, in any setting, including in a vertebrate host cell in vivo (whole organism), using a double stranded RNA molecule comprising a region with homology to a target molecule or a vector expressing the double stranded RNA molecule, which encompasses gene therapy methods and dsRNA inhibition, as well as antisense methods (particularly given the broad meaning of "homology").

The specification provides examples wherein plant genes are inhibited using dsRNA and expressed dsRNA. The specification has not provided any examples wherein a dsRNA or a vector expressing a dsRNA is delivered to a vertebrate cell in vivo (whole organism).

At the time of the instant invention, and even to date, methods of inhibiting gene expression using nucleic acids in vivo(whole organism) are highly unpredictable, mainly due to issues of how to specifically deliver a nucleic acid molecule or vector to a target cell at a concentration effective to result in a desired effect, and, in the case of gene therapy, the determination of target cell specific vectors and promoters to achieve and maintain expression of the gene. Gene therapy methods (ie. nucleic acids expressed from a vector) are further hampered by unpredictable loss of expression (see for example Branch, Crooke, Anderson and Verma et al.). The specification states that the claimed methods differ from antisense methods by acting through a different, but undefined, mechanism. Despite the mechanism, the methods claimed require that an RNA, or vector expressing said RNA, be delivered specifically to a target cell in an organism in vivo(whole organism) at a concentration effective enough to inhibit the expression of a target gene. As such, although Branch, Agrawal(TIBTech), Verma et al. and Anderson discuss issues of delivery and expression in reference to antisense methods and gene therapy vectors expressing protein products, the same art recognized issues of enablement would apply to the instantly claimed methods. The specification provides guidance with respect to delivery of double stranded RNA molecules, or vectors expressing such, into plant cells, or into plant embryos, which can

then develop into a whole plant, however, the specification does not provide any specific guidance that would enable one skilled in the art to overcome the art recognized unpredictability of specific delivery of nucleic acids (or vectors) to a target cell, or effective and sustained expression of a vector expressing such a nucleic acid in any other organism besides a plant. The guidance provided for plants would not be expected to translate into generally any other organism because methods of delivering nucleic acids in plants are very different than those for other organisms, especially vertebrates, including mammals. For example, mammals, including humans, have demonstrated an immune response triggered by even small amounts of double stranded RNA that would preclude the use of double stranded RNA in vivo (whole organism).

To practice the methods claimed, over the full scope claimed, it would require undue trial and error experimentation for the skilled artisan. Such experimentation would include the determination of how to specifically deliver a double stranded RNA or a vector to a target cell at a concentration effective enough to inhibit the expression of a target gene, the determination of an appropriate vector and enhancer-promoter combination for each target cell type "the search for such combinations is a case of trial and error for a given type of cell."(see Verma, for example p 240, columns 2 and 3), how to overcome the effects of dsRNA induced immune response.

Therefore, based on the breadth of the claims, the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of specific guidance by the inventor (beyond plants), the lack of working examples (beyond plants), and the

quantity of experimentation that would be required, it would require undue experimentation, beyond what is taught in the specification, to practice the methods as claimed, over the full scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1, 2, 6-12 and 16-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Thompson (US Patent No. 5,902,880).

Thompson discloses and claims RNA molecules wherein the molecule comprises a region of homology to a target RNA (for example, an antisense molecule) and further comprises complementary RNA regions that hybridize to form a hairpin, wherein the complementary regions are unrelated to the target molecule. The complementary regions disclosed by Thompson do not comprise plant viral RNA. Thompson further discloses vectors that express these RNA molecules and discloses transforming host cells with the vector or RNA and inhibiting the expression of a target gene in the host cell.

Therefore, Thompson anticipates claims 1, 2, 6-12 and 16-19.

Claims 1, 2, 6-12 and 16-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Thompson (US Patent No. 6,146,886).

Thompson discloses and claims RNA molecules wherein the molecule comprises a region of homology to a target RNA (for example, an antisense molecule) and further comprises complementary RNA regions that hybridize to form a hairpin, wherein the complementary regions are unrelated to the target molecule. The complementary regions disclosed by Thompson do not comprise plant viral RNA. Thompson further discloses vectors that express these RNA molecules and discloses transforming host cells with the vector or RNA and inhibiting the expression of a target gene in the host cell.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Friday 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
January 12, 2003